REMARKS

By the present amendment, Claim 28 has been cancelled. Claims 27 and 32-35 remain pending. Applicants thank the Examiner for her careful review of the instant application and for recasting the rejections in order to focus the issues. The pending claims stand rejected for allegedly being unpatentable under 35 U.S.C. §§101 and 112, first paragraph, and under 35 U.S.C. §§102 and 103 in view of several cited references. For the reasons set forth below, Applicants respectfully traverse.

Rejection under 35 U.S.C. §101 and §112

The Examiner asserts that many of the utilities asserted in the application pertain solely to nucleic acids, and that the remaining utilities asserted are not specific for the discloser PRO1800 protein. In particular, the Examiner claims that that the gene amplification data disclosed on pages 116-117 of the present application does not satisfy the utility requirement of 35 USC §101 for the polypeptide and further, that the application does not satisfy the written description requirement of 35 USC§ 112, first paragraph, for the polypeptide. Citing Pennica *et al.*, the Examiner states that "data pertaining to PRO1800 nucleic acids do not necessarily indicate anything significant regarding the claimed PRO1800 polypeptides. Thus, the data do not support the implicit assertion that PRO1800 can be used as a cancer diagnostic." The Examiner asserted that DNA amplification is not always associated with overexpression of gene product and concluded that, "significant further research would have been required of the skilled artisan to determine whether PRO1800 is overexpressed in any cancer to the extent that it could be used as a cancer diagnostic, and thus the implicitly asserted utility is not substantial."

Applicants respectfully disagree.

Evidentiary Standard

An Applicant's assertion of utility creates a presumption of utility that will be sufficient to satisfy the utility requirement of 35 U.S.C. § 101, "unless there is a reason for one skilled in the art to question the objective truth of the statement of utility or its scope." *In re Langer*, 503 F.2d 1380, 1391, 183 USPQ 288, 297 (CCPA 1974). See, also *In re Jolles*, 628 F.2d 1322, 206 USPQ 885 (CCPA 1980); *In re* Irons, 340 F.2d 974, 144 USPQ 351 (1965); *In re Sichert*, 566 F.2d 1154, 1159, 196 USPQ 209, 212-13 (CCPA 1977).

Compliance with 35 U.S.C. § 101 is a question of fact. *Raytheon v. Roper*, 724 F.2d 951, 956, 220 USPQ 592, 596 (Fed. Cir. 1983) cert. denied, 469 US 835 (1984). The evidentiary standard to be used throughout *ex parte* examination in setting forth a rejection is a preponderance of the totality of the evidence under consideration. *In re Oetiker*, 977 F.2d 1443, 1445, 24 USPQ2d 1443, 1444 (Fed. Cir. 1992). Thus, to overcome the presumption of truth that an assertion of utility by the applicant enjoys, the Examiner must establish that it is more likely than not that one of ordinary skill in the art would doubt the truth of the statement of utility. Only after the Examiner has made a proper *prima facie* showing of lack of utility does the burden of rebuttal shift to the applicant. The issue will then be decided on the totality of evidence.

A prima facie case of lack of utility has not been established

The Examiner bases the conclusion of lack of utility on a quote from Pennica *et al.* According to the quoted statement, "*WISP*-2 DNA was amplified in colon tumors, but its mRNA expression was significantly reduced in the majority of tumors compared with the expression in normal colonic mucosa from the same patient." From this, the Examiner correctly concludes that increased gene copy number does not *necessarily* result in increased protein expression. The standard, however, is not absolute certainty. The fact that in the case of a specific class of closely related molecules there seemed to be no correlation between gene amplification and the level of mRNA/protein expression, does not establish that it is more likely than not, in general, that such correlation does not exist. The Examiner has not shown whether the lack of correlation observed for the family of WISP polypeptides is typical, or is merely a discrepancy, an exception to the rule of correlation. Indeed, the working hypothesis among those skilled in the art is that, if a gene is amplified in cancer, the encoded protein is likely to be expressed at an elevated level.

Enclosed is a copy of a Declaration by J. Christopher Grimaldi, an expert in the field of cancer biology. This declaration was submitted in connection with co-pending application Serial No. 10/006,867. As stated in paragraph 5 of the declaration, "Those who work in this field are well aware that in the vast majority of cases, when a gene is over-expressed...the gene product or polypeptide will also be overexpressed." The references cited in the declaration and submitted herewith support this statement.

In addition, Applicants have previously submitted the Declarations of Audrey Goddard and Avi Ashkenazi, both of whom are experts in the field of cancer biology. As Dr. Goddard explains in paragraph 7 of her Declaration:

> It is my personal experience that the quantitative TaqMan PCR technique is technically sensitive enough to detect at least a 2-fold increase in gene copy number relative to control. It is further my considered scientific opinion that an at least 2-fold increase in gene copy number in a tumor tissue sample relative to a normal (i.e., non-tumor) sample is significant and useful in that the detected increase in gene copy number in the tumor sample relative to the normal sample serves as a basis for using relative gene copy number as quantitated by the TaqMan PCR technique as a diagnostic marker for the presence or absence of tumor in a tissue sample of unknown pathology. Accordingly, a gene identified as being amplified at least 2-fold by the quantitative TaqMan PCR assay in a tumor sample relative to a normal sample is useful as a marker for the diagnosis of cancer, for monitoring cancer development and/or for measuring the efficacy of cancer therapy.

The data presented on pages 116-117 of the present application indicate ΔCt values for the DNA encoding the PRO1800 polypeptide of greater than 1, which mean at least a 2-fold increase in gene copy number in tumor tissue samples as compared to normal tissue samples. Using a widely accepted technique, Applicants have generated data showing that the gene encoding the PRO1800 polypeptide is amplified in cancerous tissue. The general, accepted understanding in the art is that the level of protein expression would therefore also be increased.

The Examiner also states that cancerous tissue is known to be aneuploid, and a slight amplification of a gene may indicate only that the cancer tissue is aneuploid. Applicants have also previously provided the Declaration of Dr. Avi Ashkenazi, who explains that:

> An increase in gene copy number can result not only from intrachromosomal changes but also from chromosomal aneuploidy. It is important to understand that detection of gene amplification can be used for cancer diagnosis <u>even if the determination includes measurement of chromosomal aneuploidy</u>. Indeed, as long as a significant difference relative to normal tissue is detected, it is irrelevant if the signal originates from an increase in the number of gene copies per chromosome and/or an abnormal number of chromosomes. (Emphasis added.)

Ashkenazi Declaration, paragraph 5. Thus, as Dr. Ashkenazi explains, whether or not the cells exhibit aneuploidy, the presently claimed polypeptides can be used to determine whether overexpression of certain genes occurs in a cell, and thereby detect whether or not the cell is

cancerous. Accordingly, Applicants respectfully maintain that the possible aneuploidy of cancer cells is irrelevant in the use of the proteins of the present invention in detecting cancerous cells.

Applicants believe they have supplied sufficient evidence to show that there is a significant correlation between gene amplification and protein expression. However, even if one assumes *arguendo* that it is more likely than not that there is no correlation between gene amplification and increased mRNA/protein expression, a polypeptide encoded by a gene that is amplified in cancer would still have a specific and substantial utility.

As explained in paragraph 6 of the Ashkenazi Declaration:

> Even when amplification of a cancer marker gene does not result in significant over-expression of the corresponding gene product, this very absence of gene product over-expression still provides significant information for cancer diagnosis and treatment. Thus, if over-expression of the gene product does not parallel gene amplification in certain tumor types but does so in others, then parallel monitoring of gene amplification and gene product over-expression enables more accurate tumor classification and hence better determination of suitable therapy. In addition, absence of over-expression is crucial information for the practicing clinician. If a gene is amplified but the corresponding gene product is not over-expressed, the clinician accordingly will decide not to treat a patient with agents that target that gene product.

This statement is echoed by Mr. Grimaldi in his declaration at paragraph 6. Thus, given the totality of the evidence provided, Applicants submit that they have established a specific and substantial credible utility for the claimed polypeptide as a diagnostic agent. According to the PTO Utility Examination Guidelines (2001), irrefutable proof of a claimed utility is not required. Rather, a specific and substantial credible utility requires only a "reasonable" confirmation of a real world context of use. Applicants submit that they have met their burden of showing that one of skill in the art would reasonably accept the utility for the PRO1800 polypeptide set forth in the specification.

Even if a prima facie case of lack of utility had been established, it should be withdrawn on consideration of the totality of evidence

Applicants have provided several expert opinions supporting the utility of the present invention. Applicants submit that one of ordinary skill in the art would have no legitimate basis to doubt the credibility of the statements made by Mr. Grimaldi, Dr. Goddard and Dr. Ashkenazi, and must treat as true the statements made by these experts. Applicant reminds the Examiner

that "Office personnel must accept an opinion from a qualified expert that is based upon relevant facts whose accuracy is not being questioned; it is improper to disregard the opinion solely because of a disagreement over the significance or meaning of the facts offered." PTO Utility Examination Guidelines (2001).

Applicants believe that they have met their burden of establishing a specific and substantial credible utility for the claimed invention. Accordingly, Applicants respectfully request that the rejection under 35 U.S.C. §101 be withdrawn.

Rejection under 35 U.S.C. §112, first paragraph

Claims 27, 28, and 32-35 were also rejected under 35 U.S.C. §112, first paragraph as not having a specific utility. However, for the reasons outlined above in response to the rejection under 35 U.S.C. §101, Applicants believe they have established the utility of the claimed invention and therefore respectfully request withdrawal of the rejection under 35 U.S.C. §112, first paragraph.

Rejection under 35 U.S.C. §§102 and 103

Because of the allegations of the lack of utility for the claimed invention, the Examiner has accorded an effective priority date for this application of its instant filing date. Consequently, the Examiner has cited certain references as prior art against the instant claims and have alleged that the claims are unpatentable in view of these references. Applicants respectfully traverse.

Applicants submit that priority has been properly claimed to PCT/US99/28634 filed December 1, 1999. As is apparent from the discussion above, Applicants submit that the results of the gene amplification assays provide specific and substantial asserted utility for the claimed polypeptide. Since this utility was disclosed in PCT/US99/28634, the claims pending are fully entitled to the priority date of December 1, 1999.

Since the Strausberg and Furukawa references were published after December 1, 1999, these references are not available as prior art.

As for the Fransen references, Applicants submit that these references are not available as prior art either. Fransen et al. (5/1/99) disclose locus O95162, which according to the Examiner, has 99.2% identity to SEQ ID NO:2 lacking its signal peptide, i.e. residues 19-278 of SEQ ID

NO:2. Fransen et al. (5/27/99) disclose locus AF044127, which according to the Examiner has 99.3% identity to the entirety of SEQ ID NO:2. Applicants maintain their position that since neither Fransen reference discloses the full length sequence of SEQ ID NO:2, neither reference anticipates the claimed invention. Further, since no evidence has been presented of a motivation or suggestion in the references themselves or in the general knowledge in the art to modify the sequences disclosed in the cited references to obtain the claimed polypeptides, the cited references fail to render obvious the claimed invention. Nevertheless, Applicants submit that they were in possession of the claimed invention prior to the prior to the May 1999 dates of the cited references, so as to remove the Fransen references as prior art.

Applicants are also entitled to priority to U.S. Provisional Application No. 60/112851 filed on December 16, 1998. This application includes the disclosure of the full length sequence of SEQ ID NO:2. As the December 16, 1998 date precedes the May 1999 dates of the Fransen references, Applicants have shown possession of the claimed invention prior to both Fransen references.

The well-established "Stempel Doctrine" stands for the proposition that a patent applicant can effectively swear back of and remove a cited prior art reference by showing that he or she made that portion of the claimed invention that is disclosed in the prior art reference. (*In re Stempel*, 113 USPQ 77 (CCPA 1957)). In other words, a patent applicant need not demonstrate that he or she made the entire claimed invention in order to remove a cited prior art reference. He or she need only demonstrate prior possession of that portion of his or her claimed invention that is disclosed in the prior art reference and nothing more.

The Stempel Doctrine was extended to cases where a reference disclosed the claimed compound but failed to disclose a sufficient utility for it in *In re Moore*, 170 USPQ 260 (CCPA 1971). More specifically, the patent applicant (Moore) claimed a specific chemical compound called PFDC. In support of a rejection of the claim under 35 U.S.C. § 102, the Examiner cited a reference which disclosed the claimed PFDC compound, but did not disclose a utility for that compound. Applicant Moore filed a declaration under 37 C.F.R. § 1.131 demonstrating that he had made the PFDC compound before the effective date of the cited prior art reference, <u>even though he had not yet established a utility for that compound</u>. The lower court found the 131 declaration ineffective to swear back of and remove the cited reference, reasoning that since

Moore had not established a utility for the PFDC compound prior to the effective date of the cited prior art reference, he had not yet completed his "invention".

On appeal, however, the CCPA reversed the lower court decision and indicated that the 131 declaration filed by Moore was sufficient to remove the cited reference. The CCPA relied on the established Stempel Doctrine to support its decision, stating:

> An applicant need **not** be required to show [in a declaration under 37 C.F.R. § 1.131] any more acts with regard to the subject matter claimed that can be carried out by one of ordinary skill in the pertinent art following the description contained in the reference....the determination of a practical utility when one is not obvious need **not** have been accomplished prior to the date of a reference unless the reference also teaches how to use the compound it describes. (Id. at 267, emphasis added).

Thus, *In re Moore* confirms the Stempel Doctrine, holding that in order to effectively remove a cited reference with a declaration under 37 C.F.R. § 1.131, an applicant need only show that portion of his or her claimed invention that appears in the cited reference. Moreover, *In re Moore* stands for the proposition that when a cited reference discloses a claimed chemical compound either absent a utility or with a utility that is different from the one appearing in the claims at issue, a patent applicant can effectively swear back of that reference by simply showing prior possession of the claimed chemical compound. In other words, under this scenario, the patent applicant need not demonstrate that he or she had discovered a patentable utility for the claimed chemical compound prior to the effective date of the prior art reference.

While these cases discuss the ability to effectively swear back of the cited reference by way of a 131 declaration, Applicants submit that the same reasoning applies here, where the application claims priority back to a disclosure that predates the cited references. Applicants demonstrated, by means of the disclosure in their provisional application filed December 16, 1998, that they were in possession of so much of the claimed invention, i.e. SEQ ID NO:2, as disclosed in the Fransen references dated May 1999. Thus, Applicants respectfully submit that the cited references are not available as prior art, and request that the rejections under 35 USC §§102 and 103 be removed.

CONCLUSION

The present application is believed to be in *prima facie* condition for allowance, and an early action to that effect is respectfully solicited. Applicants invite the Examiner to call the undersigned if any issues may be resolved through a telephonic conversation.

Please charge any necessary fees, including any fees for any extensions of time, to Deposit Account No. 11-1410.

Respectfully submitted,

KNOBBE, MARTENS, OLSON & BEAR, LLP

Dated: Apr May 7, 2004

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